REMARKS

Applicants submit herewith a Request for Continued Examination in this application along with an amendment. Applicants have canceled all the claims from the application without prejudice or disclaimer and new claims 25-41 have been added. These claims essentially parallel claims 1-4, 7-10, 12, 13, 18 and 19 and are fully supported by Applicants' specification. Applicants most respectfully submit that all of the claims now present in the application are in full compliance with 35 U.S.C. 112 and are clearly patentable over the references of record.

The rejection of claim 5 under 35 U.S.C. 112, second paragraph, as being indefinite has been carefully considered but is believed to be obviated due to the cancellation of claim 5 from the application without including a corresponding claim containing the rejected language from claim 5 in the new claims submitted herewith. Accordingly, it is most respectfully requested that this rejection be withdrawn.

The rejection of claims 1-3, 8 and 9 under 35 U.S.C. 103 as being unpatentable over Hirao et al. and also the rejection of claims 7, 12, 13, 18 and 19 has been carefully considered but is most respectfully traversed in view of the amendments to the claims following comments. With respect to the claims, Applicants note that claim 25 is a combination of original claims 1 and 6. Claim 6 has not been acted on the merits as it was withdrawn from consideration as directed to a patentably distinct species. Thus, is is believed that all of the claims now present in the application are clearly patentable over the references of record by the inclusion of this patentably distinct limitation into all of the claims now or record.

The claims previously presented were rejected on the basis of Hirao et al. either alone or in combination with Douglas et al.

Hirao et al. describes a process of shaping anhydrous crystals of maltitol which have utility in a number of instances as listed at column 7. It is noted that this patent is primarily concerned with the use of maltitol in foodstuffs, i.e., a different technical field to the current invention. Whilst it is accepted that there are references to pharmaceutical applications within Hirao, a person skilled in the art would not consider

maltitol for use in an inhalation product. In support of this assertion we enclose an abstract from the Handbook of Pharmaceutical Excipients (Pharmaceutical Press, 3rd Edition, page 313). It is noted that maltitol is only known in the pharmaceutical art as bulk sweetener for oral dosage forms. Applicants maintain that there is nothing to suggest that the product obtained from the process described in Hirao et al. is suitable as a component of an inhalation pharmaceutical product.

Hirao et al. is clearly related to the solving of a very specific problem associated with maltitol i.e. that it is extremely hygroscopic and deliquescent, and difficult to prepare into a powder (column 1). The only explanation offered by the Examiner as to what would motivate a skilled person to replace, for example, maltitol with lactose monohydrate (as per the Examiner's assertion on page 9 of the Official Action) is that they are both sugar alcohols. The teaching of Hirao et al. does not make this connection in terms of equivalence of properties as noted above so why would a person working in a different technical field on a totally different problem? Applicants maintain that the conclusion drawn by the Examiner can only be reached by hindsight reasoning.

Furthermore, the Examiner has dismissed certain feature of claim 1, namely specific viscosity ranges, as being of no relevance on the basis that the same results of the process are desired i.e., "a crystalline composition that is non-hygroscopic, free flowing and can be in any desired size and shape" (page 4). Applicants do not accept that a term such as, for example, "free-flowing" has a recognized meaning particularly when reference is being made to different technical fields. It is certainly not, by itself, enough to equate a crystallization process for a food additive with that of a crystallization process for a component of an inhaled pharmaceutical composition. On this basis, Applicants most respectfully believe that the Examiner's analysis is in error. Accordingly, it is most respectfully requested that this rejection be withdrawn.

The rejection of claims 4, 5 and 10 under 35 U.S.C. 103(a) as being unpatentable over Hirao et al, and Douglas et al. has been carefully considered but is most respectfully traversed in view of the above comments with respect to Hirao and the following comments with respect to Douglas et al.

Douglas et al. describes a ranitidine composition which is substantially free of bitter taste. This reference is being used in combination with Hirao et al. for rejection originally filed claims 4, 5 and 10 (4 and 8 only in amended claims). For reasons stated above, Applicants believe that as claim 1 is non-obvious over the prior art then any claims dependent thereon are also non-obvious. No further arguments are being submitted to further rebut this rejection over and above those made in our amendment filed May 14, 2002. It is therefore most respectfully requested that this rejection be withdrawn.

In view of the above comments and further amendments to the claims, favorable reconsideration and allowance of all the claims now present in the application are most respectfully requested.

Respectfully submitted,
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Maltitol

1. Nonproprietary Names

BP: Maltitol

PhEur: Maltitolum

2. Synonyms

Amalty; E965; hydrogenated maltose; *Malbit*; *Maltisorb*; *Maltit*; D-maltitol.

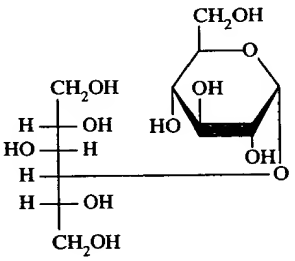
3. Chemical Name And Cas Registry Number

4-*O*-α-D-Glucopyranosyl-D-glucitol [585-88-6]

4. Empirical Formula and Molecular Weight

$C_{12}H_{24}O_{11}$ 344.32

5. Structural Formula



6. Functional Category

Coating agent; diluent; granulating agent; suspending agent; sweetening agent; viscosity-increasing agent.

7. Applications in Pharmaceutical Formulation or Technology

Maltitol is widely used in the pharmaceutical industry in the formulation of oral dosage forms. It is a noncariogenic bulk sweetener, as sweet as sucrose, well adapted as a diluent for the different oral dosage forms, wet granulation, and hard coating.

8. Description

Maltitol occurs as a white, odorless, sweet, crystalline powder. It is a disaccharide consisting of one glucose unit linked with one sorbitol unit via an alpha (1,4) bond.

9. Pharmacopeial Specifications

Test	PhEur
Identification	+
Characters	+
Appearance of solution	+
Acidity or alkalinity	+
Specific optical rotation (5% solution)	+105.5° to +108.5°
Reducing sugars	+
Chlorides	≤ 50 ppm
Sulfates	≤ 100 ppm
Lead	≤ 0.5 ppm
Nickel	≤ 1 ppm
Water	≤ 1%
Sulfated ash	≤ 0.1%
Assay (dried basis)	98-102%

10. Typical Properties

Compressibility: 9.5%

Density (bulk): 0.79 g/cm^3

Density (tapped): 0.95 g/cm^3

Flowability (funnel test): 5 seconds

Melting point: 148-151°C

Particle size distribution: 95% ≤ 500 μm, 40% ≥ 100 μm in size for *Maltisorb P200* (Roquette); 95% ≤ 200 μm, 50% ≥ 100 μm in size for *Maltisorb P90* (Roquette).

Solubility: freely soluble in water.

11. Stability And Storage Conditions

Maltitol has good thermal and chemical stability. When heated at temperatures above 200°C, decomposition begins (depending on time, temperature, and other prevailing conditions). Maltitol does not undergo browning reactions with amino acids, and absorbs atmospheric moisture only at relative humidities of 89% and above, at 20°C.

12. Incompatibilities

–

13. Method of Manufacture

Maltitol is obtained from hydrogenated maltose syrup. Starch is hydrolyzed to yield a high-concentration maltose syrup which is hydrogenated with a catalyst. After purification and concentration, the syrup is crystallized.

14. Safety

Maltitol is used in oral pharmaceutical formulations, confectionery, and food products and is considered to be noncarcinogenic. It is generally regarded as a nontoxic, nonallergenic, and nonirritant material.

Digestion of maltitol follows two different metabolic pathways: absorption in the small intestine and fermentation in

the large intestine (colon). These two metabolic pathways must thus be considered when evaluating the energy value.

The hydrolysis of maltitol in the small intestine releases sorbitol and glucose. Glucose is actively transported and rapidly absorbed, whereas sorbitol absorption is passive. The nonabsorbed sorbitol and nonhydrolyzed maltitol are fermented by the microflora in the colon. The relative importance of the two absorption pathways depends on numerous individual factors and is related to the quantity of maltitol ingested. Excessive oral consumption (>50 g daily) may cause flatulence and diarrhea.

Maltitol exhibits a low glycemic index and can therefore, under medical supervision, have a place in the diet of diabetic patients. The intake of maltitol must be taken into account for the calculation of the daily glucidic allowance.

The WHO in considering the safety of maltitol did not set a value for the acceptable daily intake since the levels used in food to achieve a desired effect were not considered a hazard to health.[1,2]

15. Handling Precautions

Observe normal precautions appropriate to circumstances and quantity of material handled. Eye protection and gloves are recommended.

16. Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in oral pharmaceutical formulations.

17. Pharmacopeias

Eur.

18. Related Substances

Maltitol solution.

19. Comments

Maltitol is not fermented by oral bacteria and is neither acidogenic nor cariogenic.

20. Specific References

1. FAO/WHO. Evaluation of certain food additives and contaminants: thirty-third report of the joint FAO/WHO expert committee on food additives. *Tech Rep Ser Wld Hlth Org* 1989; No. 776.
2. FAO/WHO. Evaluation of certain food additives and contaminants: forty-sixth report of the joint FAO/WHO expert committee on food additives. *Tech Rep Ser Wld Hlth Org* 1997; No. 868.

21. General References

Moskowitz AH. Maltitol and hydrogenated starch hydrolysate. In: Nabors LO, Gelardi RC, editors. *Alternative Sweeteners*, 2nd edition. New York, Marcel Dekker, 1991; 259-282.

Portman MO, Kilcast D. Psycho-physical characterization of new sweeteners of commercial importance for the EC food industry. *Food Chemistry* 1996; 56(3): 291-302.

22. Authors

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